NDA 20-243/S-021 SEP 2 8 2000

Solvay Pharmaceuticals
Attention: J. Greg Perkins, Ph.D.
Vice President Regulatory Science
901 Sawyer Road
Marietta, Georgia 30062

Dear Dr. Perkins:

Please refer to your supplemental new drug application dated and received December 2, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Luvox (fluvoxamine maleate) 25 mg, 50 mg, and 100 mg Tablets.

Additionally, we acknowledge receipt of your submissions dated May 31, and June 30, 2000.

Reference is also made to an Agency letter dated March *25,* 1997, providing for the approval of supplemental application S-006 to use Luvox to treat obsessive compulsive disorder in the pediatric population. This letter also committed that Solvay explore further the effects of Luvox in obsessive compulsive disorder (OCD) patients between the ages of 12— 17 years old as a Phase 4 commitment.

We additionally refer to a series of faxes dated September 21,24, and 26, 2000 in which labeling for this supplemental application, S-021, was agreed upon by Solvay and the Agency.

This supplemental new drug application provides for revised labeling of Luvox based upon the results of a long-term, open-label safety study and a pharmacokinetic study in children and adolescents with OCD.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, this supplemental application is approved effective on the date of this letter.

Additionally, this data completely fulfills your Phase 4 commitment for S-006 as enumerated in our March 25, 1997, Agency letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

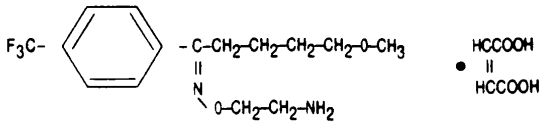
Please submit 20 paper copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format- NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-243/S-021 ". Approval of this submission by FDA is not required before the labeling is used.

LUVOX®
(Fluvoxamine Maleate) Tablets
25 mg, 50 mg and 100 mg

DESCRIPTION

Fluvoxamine maleate is a selective serotonin (5-HT) reuptake inhibitor (SSRI) belonging to a new chemical series, the 2-aminoethyl oxime ethers of aralkylketones. It is chemically unrelated to other SSRIs and clomipramine. It is chemically designated as 5-methoxy-4'-(trifluoromethyl)valerophenone-(E)-O-(2-aminoethyl)oxime maleate (1:1) and has the empirical formula $C_{15}H_{21}O_2N_2F_3 \bullet C_4H_4O_4$. Its molecular weight is 434.4.

The structural formula is:



Fluvoxamine maleate is a white or off white, odorless, crystalline powder which is sparingly soluble in water, freely soluble in ethanol and chloroform and practically insoluble in diethyl ether.

LUVOX® (Fluvoxamine Maleate) Tablets are available in 25 mg, 50 mg and 100 mg strengths for oral administration. In addition to the active ingredient, fluvoxamine maleate, each tablet contains the following inactive ingredients: carnauba wax, hydroxypropyl methylcellulose, mannitol, polyethylene glycol, polysorbate 80, pregelatinized starch (potato), silicon dioxide, sodium stearyl fumarate, starch (corn), and titanium dioxide. The 50 mg and 100 mg tablets also contain synthetic iron oxides.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of fluvoxamine maleate in Obsessive Compulsive Disorder is presumed to be linked to its specific serotonin reuptake inhibition in brain neurons. In preclinical studies, it was found that fluvoxamine inhibited neuronal uptake of serotonin.

In *in vitro* studies fluvoxamine maleate had no significant affinity for histaminergic, alpha or beta adrenergic, muscarinic, or dopaminergic receptors. Antagonism of some of these receptors is thought to be associated with various sedative, cardiovascular, anticholinergic, and extrapyramidal effects of some psychotropic drugs.

Pharmacokinetics

Bioavailability: The absolute bioavailability of fluvoxamine maleate is 53%. Oral bioavailability is not significantly affected by food.

In a dose proportionality study involving fluvoxamine maleate at 100, 200 and 300 mg/day for 10 consecutive days in 30 normal volunteers, steady state was achieved after about a week of dosing. Maximum plasma concentrations at steady state occurred within 3-8 hours of dosing and reached concentrations averaging 88, 283 and 546 ng/mL, respectively. Thus, fluvoxamine had nonlinear pharmacokinetics over this dose range, i.e., higher doses of fluvoxamine maleate produced disproportionately higher concentrations than predicted from the lower dose.

Distribution/Protein Binding: The mean apparent volume of distribution for fluvoxamine is approximately 25 L/kg, suggesting extensive tissue distribution.

Approximately 80% of fluvoxamine is bound to plasma protein, mostly albumin, over a concentration range of 20 to 2000 ng/mL.

Metabolism: Fluvoxamine maleate is extensively metabolized by the liver; the main metabolic routes are oxidative demethylation and deamination. Nine metabolites were identified following a 5 mg radiolabelled dose of fluvoxamine maleate, constituting approximately 85% of the urinary excretion products of fluvoxamine. The main human metabolite was fluvoxamine acid which, together with its N-acetylated analog, accounted for about 60% of the urinary excretion products. A third metabolite, fluvoxethanol, formed by oxidative deamination, accounted for about 10%. Fluvoxamine acid and fluvoxethanol were tested in an *in vitro* assay of serotonin and norepinephrine reuptake inhibition in rats; they were inactive except for a weak effect of the former metabolite on inhibition of serotonin uptake (1-2 orders of magnitude less potent than the parent compound). Approximately 2% of fluvoxamine was excreted in urine unchanged. (See **PRECAUTIONS - Drug Interactions**)

Elimination: Following a ^{14}C-labelled oral dose of fluvoxamine maleate (5 mg), an average of 94% of drug-related products was recovered in the urine within 71 hours.

The mean plasma half-life of fluvoxamine at steady state after multiple oral doses of 100 mg/day in healthy, young volunteers was 15.6 hours.

Elderly Subjects: In a study of LUVOX® Tablets at 50 and 100 mg comparing elderly (ages 66-73) and young subjects (ages 19-35), mean maximum plasma concentrations in the elderly were 40% higher. The multiple dose elimination half-life of fluvoxamine was 17.4 and 25.9 hours in the elderly compared to 13.6 and 15.6 hours in the young subjects at steady state for 50 and 100 mg doses, respectively.

In elderly patients, the clearance of fluvoxamine was reduced by about 50% and, therefore, LUVOX® Tablets should be slowly titrated during initiation of therapy.

Pediatric Subjects: The multiple-dose pharmacokinetics of fluvoxamine were determined in male and female children (ages 6-11) and adolescents (ages 12-17). Steady-state plasma fluvoxamine concentrations were 2-3 fold higher in children than in adolescents. AUC and Cmax in children were 1.5- to 2.7-fold higher than that in adolescents (see table below). As in adults, both children and adolescents exhibited nonlinear multiple-dose pharmacokinetics. Female children showed significantly higher AUC (0-12) and Cmax compared to male children and, therefore, lower doses of LUVOX® Tablets may produce therapeutic benefit (see table below). No gender differences were observed in adolescents. Steady-state plasma fluvoxamine concentrations were similar in adults and adolescents at a dose of 300 mg/day, indicating that fluvoxamine exposure was similar in these two populations (see table below). Dose adjustment in adolescents (up to the adult maximum dose of 300 mg) may be indicated to achieve therapeutic benefit.

Comparison of Mean (SD) fluvoxamine pharmacokinetic parameters between children, adolescents and adults

Pharmacokinetic Parameter (body weight corrected)	Dose = 200 mg/day (100 mg bid)		Dose = 300 mg/day (150 mg bid)	
	Children (n=10)	Adolescent (n=17)	Adolescents (n= 13)	Adults (n=16)
AUC0-12 (ng.h/ml/kg)	155.1 (160.9)	43.9 (27.9)	69.6 (46.6)	59.4 (40.9)
Cmax (ng/ml/kg)	14.8 (14.9)	4.2 (2.6)	6.7 (4.2)	5.7 (3.9)
Cmin (ng/ml/kg)	11.0 (11.9)	2.9 (2.0)	4.8 (3.8)	4.6 (3.2)

Comparison of Mean (SD) fluvoxamine pharmacokinetic parameters between male and female children (6-11 years)

Pharmacokinetic Parameter (body weight corrected)	Dose = 200 mg/day (100 mg bid)

	Male Children (n=7)	Female children (n= 3)
AUC0-12 (ng.h/ml/kg)	95.8 (83.9)	293.5 (233.0)
Cmax (ng/ml/kg)	9.1 (7.6)	28.1 (21.1)
Cmin (ng/ml/kg)	6.6 (6.1)	21.2 (17.6)

Hepatic and Renal Disease: A cross study comparison (healthy subjects vs. patients with hepatic dysfunction) suggested a 30% decrease in fluvoxamine clearance in association with hepatic dysfunction. The mean minimum plasma concentrations in renally impaired patients (creatinine clearance of 5 to 45 mL/min) after 4 and 6 weeks of treatment (50 mg bid, N=13) were comparable to each other, suggesting no accumulation of fluvoxamine in these patients. (See **PRECAUTIONS - *Use in Patients with Concomitant Illness***)

Clinical Trials

Adult OCD Studies: The effectiveness of LUVOX® Tablets for the treatment of Obsessive Compulsive Disorder (OCD) was demonstrated in two 10-week multicenter, parallel group studies of adult outpatients. Patients in these trials were titrated to a total daily fluvoxamine maleate dose of 150 mg/day over the first two weeks of the trial, following which the dose was adjusted within a range of 100-300 mg/day (on a bid schedule), on the basis of response and tolerance. Patients in these studies had moderate to severe OCD (DSM-III-R), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), total score of 23. Patients receiving fluvoxamine maleate experienced mean reductions of approximately 4 to 5 units on the Y-BOCS total score, compared to a 2 unit reduction for placebo patients.

The following table provides the outcome classification by treatment group on the Global Improvement item of the Clinical Global Impressions (CGI) scale for both studies combined.

OUTCOME CLASSIFICATION (%) ON CGI-GLOBAL IMPROVEMENT ITEM FOR COMPLETERS IN POOL OF TWO ADULT OCD STUDIES		
Outcome Classification	**Fluvoxamine (N = 120)**	**Placebo (N = 134)**
Very Much Improved	13%	2%
Much Improved	30%	10%
Minimally Improved	22%	32%
No Change	31%	51%
Worse	4%	6%

Exploratory analyses for age and gender effects on outcomes did not suggest any differential responsiveness on the basis of age or sex.

Pediatric OCD Study: The effectiveness of LUVOX® Tablets for the treatment of OCD was also demonstrated in a 10-week multicenter, parallel group study in a pediatric outpatient population (children and adolescents, ages 8-17). Patients in this study were titrated to a total daily fluvoxamine dose of approximately 100 mg/day over the first two weeks of the trial, following which the dose was adjusted within a range of 50-200 mg/day (on a bid schedule) on the basis of response and tolerance. All patients had moderate-to-severe OCD (DSM-III-R) with mean baseline ratings on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) total score of 24. Patients receiving fluvoxamine maleate experienced mean reductions of approximately six units on the CY-BOCS total score, compared to a three-unit reduction for placebo patients.

The following table provides the outcome classification by treatment group on the Global Improvement item of the Clinical Global Impression (CGI) scale for the pediatric study.

OUTCOME CLASSIFICATION (%) ON CGI-GLOBAL IMPROVEMENT ITEM FOR COMPLETERS IN PEDIATRIC STUDY		
Outcome Classification	**Fluvoxamine (N= 38)**	**Placebo (N= 36)**
Very Much Improved	21%	11%
Much Improved	18%	17%
Minimally Improved	37%	22%
No Change	16%	44%
Worse	8%	6%

Post hoc exploratory analyses for gender effects on outcomes did not suggest any differential responsiveness on the basis of gender. Further exploratory analyses revealed a prominent treatment effect in the 8-11 age group and essentially no effect in the 12-17 age group. While the significance of these results is not clear, the 2-3 fold higher steady state plasma fluvoxamine concentrations in children compared to adolescents (see Pharmacokinetics) is suggestive that decreased exposure in adolescents may have been a factor, and dose adjustment in adolescents (up to the adult maximum dose of 300 mg) may be indicated to achieve therapeutic benefit.

INDICATIONS AND USAGE

LUVOX® Tablets are indicated for the treatment of obsessions and compulsions in patients with Obsessive Compulsive Disorder (OCD), as defined in the DSM-III-R. The obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of LUVOX® Tablets was established in three 10-week trials with obsessive compulsive outpatients with the diagnosis of Obsessive Compulsive Disorder as defined in DSM-III-R. (See **Clinical Trials** under **CLINICAL PHARMACOLOGY**.)

Obsessive Compulsive Disorder is characterized by recurrent and persistent ideas, thoughts, impulses or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

The effectiveness of LUVOX® Tablets for long-term use, i.e., for more than 10 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use LUVOX® Tablets for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient. (See **DOSAGE AND ADMINISTRATION**)

CONTRAINDICATIONS

Co-administration of thioridazine, terfenadine, astemizole, cisapride, or pimozide with LUVOX® Tablets is contraindicated (see **WARNINGS** and **PRECAUTIONS**).

LUVOX® Tablets are contraindicated in patients with a history of hypersensitivity to fluvoxamine maleate.

WARNINGS

Potential for Interaction with Monoamine Oxidase Inhibitors

In patients receiving another serotonin reuptake inhibitor drug in combination with monoamine oxidase inhibitors (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have discontinued that drug and have been started on a MAOI. Some cases presented

with features resembling neuroleptic malignant syndrome. Therefore, it is recommended that LUVOX® Tablets not be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. After stopping LUVOX® Tablets, at least 2 weeks should be allowed before starting a MAOI.

Potential Interaction with Thioridazine
The effect of fluvoxamine (25 mg bid for one week) on thioridazine steady-state concentrations was evaluated in 10 male inpatients with schizophrenia. Concentrations of thioridazine and its two active metabolites, mesoridazine and sulforidazine, increased threefold following co-administration of fluvoxamine.

Thioridazine administration produces a dose-related prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsade de pointes-type arrhythmias, and sudden death. It is likely that this experience underestimates the degree of risk that might occur with higher doses of thioridazine. Moreover, the effect of fluvoxamine may be even more pronounced when it is administered at higher doses.

Therefore, fluvoxamine and thioridazine should not be co-administered (see CONTRAINDICATIONS and PRECAUTIONS).

Potential Terfenadine, Astemizole, Cisapride, and Pimozide Interactions
Terfenadine, astemizole, cisapride, and pimozide are all metabolized by the cytochrome P450IIIA4 isozyme, and it has been demonstrated that ketoconazole, a potent inhibitor of IIIA4, blocks the metabolism of these drugs, resulting in increased plasma concentrations of parent drug. Increased plasma concentrations of terfenadine, astemizole, cisapride, and pimozide cause QT prolongation and have been associated with torsades de pointes-type ventricular tachycardia, sometimes fatal. As noted below, a substantial pharmacokinetic interaction has been observed for fluvoxamine in combination with alprazolam, a drug that is known to be metabolized by the IIIA4 isozyme. Although it has not been definitively demonstrated that fluvoxamine is a potent IIIA4 inhibitor, it is likely to be, given the substantial interaction of fluvoxamine with alprazolam. Consequently, it is recommended that fluvoxamine not be used in combination with either terfenadine, astemizole, cisapride, or pimozide (see CONTRAINDICATIONS and PRECAUTIONS).

Other Potentially Important Drug Interactions
(Also see **PRECAUTIONS - Drug Interactions**)

Benzodiazepines: Benzodiazepines metabolized by hepatic oxidation (e.g., alprazolam, midazolam, triazolam, etc.) should be used with caution because the clearance of these drugs is likely to be reduced by fluvoxamine. The clearance of benzodiazepines metabolized by glucuronidation (e.g., lorazepam, oxazepam, temazepam) is unlikely to be affected by fluvoxamine.

Alprazolam - When fluvoxamine maleate (100 mg qd) and alprazolam (1 mg qid) were co-administered to steady state, plasma concentrations and other pharmacokinetic parameters (AUC, C_{max}, $T_{½}$) of alprazolam were approximately twice those observed when alprazolam was administered alone; oral clearance was reduced by about 50%. The elevated plasma alprazolam concentrations resulted in decreased psychomotor performance and memory. This interaction, which has not been investigated using higher doses of fluvoxamine, may be more pronounced if a 300 mg daily dose is co-administered, particularly since fluvoxamine exhibits non-linear pharmacokinetics over the dosage range 100-300 mg. If alprazolam is co-administered with LUVOX® Tablets, the initial alprazolam dosage should be at least halved and titration to the lowest effective dose is recommended. No dosage adjustment is required for LUVOX® Tablets.

Diazepam - The co-administration of LUVOX® Tablets and diazepam is generally not advisable. Because fluvoxamine reduces the clearance of both diazepam and its active metabolite, N-

desmethyldiazepam, there is a strong likelihood of substantial accumulation of both species during chronic co-administration.

Evidence supporting the conclusion that it is inadvisable to co-administer fluvoxamine and diazepam is derived from a study in which healthy volunteers taking 150 mg/day of fluvoxamine were administered a single oral dose of 10 mg of diazepam. In these subjects (N=8), the clearance of diazepam was reduced by 65% and that of N-desmethyldiazepam to a level that was too low to measure over the course of the 2 week long study.

It is likely that this experience significantly underestimates the degree of accumulation that might occur with repeated diazepam administration. Moreover, as noted with alprazolam, the effect of fluvoxamine may even be more pronounced when it is administered at higher doses.

Accordingly, diazepam and fluvoxamine should not ordinarily be co-administered.

Theophylline: The effect of steady-state fluvoxamine (50 mg bid) on the pharmacokinetics of a single dose of theophylline (375 mg as 442 mg aminophylline) was evaluated in 12 healthy non-smoking, male volunteers. The clearance of theophylline was decreased approximately three-fold. Therefore, if theophylline is co-administered with fluvoxamine maleate, its dose should be reduced to one third of the usual daily maintenance dose and plasma concentrations of theophylline should be monitored. No dosage adjustment is required for LUVOX® Tablets.

Warfarin: When fluvoxamine maleate (50 mg tid) was administered concomitantly with warfarin for two weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Thus patients receiving oral anticoagulants and LUVOX® Tablets should have their prothrombin time monitored and their anticoagulant dose adjusted accordingly. No dosage adjustment is required for LUVOX® Tablets.

PRECAUTIONS

General*Activation of Mania/Hypomania:* During premarketing studies involving primarily depressed patients, hypomania or mania occurred in approximately 1% of patients treated with fluvoxamine. In a ten week pediatric OCD study, 2 out of 57 patients (4%) treated with fluvoxamine experienced manic reactions, compared to none of 63 placebo patients. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, LUVOX® Tablets should be used cautiously in patients with a history of mania.

Seizures: During premarketing studies, seizures were reported in 0.2% of fluvoxamine-treated patients. LUVOX® Tablets should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Suicide: The possibility of a suicide attempt is inherent in patients with depressive symptoms, whether these occur in primary depression or in association with another primary disorder such as OCD. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for LUVOX® Tablets should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Hyponatremia: Several cases of hyponatremia have been reported. In cases where the outcome was known, the hyponatremia appeared to be reversible when fluvoxamine was discontinued. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or with concomitant conditions that might cause hyponatremia. In patients receiving LUVOX® Tablets and suffering from Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH), displacement syndromes, edematous states, adrenal disease or conditions of fluid loss, it is recommended that serum electrolytes, especially sodium as well as BUN and plasma creatinine, be monitored regularly.

Use in Patients with Concomitant Illness: Closely monitored clinical experience with LUVOX® Tablets in patients with concomitant systemic illness is limited. Caution is advised in administering LUVOX® Tablets to patients with diseases or conditions that could affect hemodynamic responses or metabolism.

LUVOX® Tablets have not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from many clinical studies during the product's premarketing testing. Evaluation of the electrocardiograms for patients with depression or OCD who participated in premarketing studies revealed no differences between fluvoxamine and placebo in the emergence of clinically important ECG changes.

In patients with liver dysfunction, fluvoxamine clearance was decreased by approximately 30%. LUVOX® Tablets should be slowly titrated in patients with liver dysfunction during the initiation of treatment.

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe LUVOX® Tablets:

***Interference with Cognitive or Motor Performance*:** Since any psychoactive drug may impair judgement, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are certain that LUVOX® Tablets therapy does not adversely affect their ability to engage in such activities.

Pregnancy: Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy with LUVOX® Tablets.

***Nursing*:** Patients receiving LUVOX® Tablets should be advised to notify their physicians if they are breast feeding an infant. (See **PRECAUTIONS - Nursing Mothers**)

***Concomitant Medication*:** Patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for clinically important interactions with LUVOX® Tablets.

Alcohol: As with other psychotropic medications, patients should be advised to avoid alcohol while taking LUVOX® Tablets.

Allergic Reactions: Patients should be advised to notify their physicians if they develop a rash, hives, or a related allergic phenomenon during therapy with LUVOX® Tablets.

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

Potential Interactions with Drugs that Inhibit or are Metabolized by Cytochrome P450 Isozymes: Multiple hepatic cytochrome P450 (CYP450) enzymes are involved in the oxidative biotransformation of a large number of structurally different drugs and endogenous compounds. The available knowledge concerning the relationship of fluvoxamine and the CYP450 enzyme system has been obtained mostly from pharmacokinetic interaction studies conducted in healthy volunteers, but some preliminary *in vitro* data are also available. Based on a finding of substantial interactions of fluvoxamine with certain of these drugs (see later parts of this section and also **WARNINGS** for details) and limited *in vitro* data for the IIIA4 isozyme, it appears that fluvoxamine inhibits the following isozymes that are known to be involved in the metabolism of the listed drugs:

IA2	**IIC9**	**IIIA4**
Warfarin	Warfarin	Alprazolam
Theophylline		

Propranolol		

In vitro data suggest that fluvoxamine is a relatively weak inhibitor of the IID6 isozyme.

Approximately 7% of the normal population has a genetic defect that leads to reduced levels of activity of cytochrome P450IID6 isozyme. Such individuals have been referred to as "poor metabolizers" (PM) of drugs such as debrisoquin, dextromethorphan, and tricyclic antidepressants. While none of the drugs studied for drug interactions significantly affected the pharmacokinetics of fluvoxamine, an *in vivo* study of fluvoxamine single-dose pharmacokinetics in 13 PM subjects demonstrated altered pharmacokinetic properties compared to 16 "extensive metabolizers" (EM): mean Cmax, AUC, and half-life were increased by 52%, 200%, and 62%, respectively, in the PM compared to the EM group. This suggests that fluvoxamine is metabolized, at least in part, by IID6 isozyme. Caution is indicated in patients known to have reduced levels of P450IID6 activity and those receiving concomitant drugs known to inhibit this isozyme (e.g. quinidine).

The metabolism of fluvoxamine has not been fully characterized and the effects of potent P450 isozyme inhibition, such as the ketoconazole inhibition of IIIA4, on fluvoxamine metabolism have not been studied.

A clinically significant fluvoxamine interaction is possible with drugs having a narrow therapeutic ratio such as terfenadine, astemizole, cisapride, or pimozide, warfarin, theophylline, certain benzodiazepines and phenytoin. If LUVOX® Tablets are to be administered together with a drug that is eliminated via oxidative metabolism and has a narrow therapeutic window, plasma levels and/or pharmacodynamic effects of the latter drug should be monitored closely, at least until steady-state conditions are reached (See **CONTRAINDICATIONS** and **WARNINGS**).

CNS Active Drugs:

Monoamine Oxidase Inhibitors: See **WARNINGS**

Alprazolam: See **WARNINGS**

Diazepam: See **WARNINGS**

Alcohol: Studies involving single 40 g doses of ethanol (oral administration in one study and intravenous in the other) and multiple dosing with fluvoxamine maleate (50 mg bid) revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of the other.

Carbamazepine: Elevated carbamazepine levels and symptoms of toxicity have been reported with the co-administration of fluvoxamine maleate and carbamazepine.

Clozapine: Elevated serum levels of clozapine have been reported in patients taking fluvoxamine maleate and clozapine. Since clozapine related seizures and orthostatic hypotension appear to be dose related, the risk of these adverse events may be higher when fluvoxamine and clozapine are co-administered. Patients should be closely monitored when fluvoxamine maleate and clozapine are used concurrently.

Lithium: As with other serotonergic drugs, lithium may enhance the serotonergic effects of fluvoxamine and, therefore, the combination should be used with caution. Seizures have been reported with the co-administration of fluvoxamine maleate and lithium.

Lorazepam: A study of multiple doses of fluvoxamine maleate (50 mg bid) in healthy male volunteers (N=12) and a single dose of lorazepam (4 mg single dose) indicated no significant pharmacokinetic interaction. On average, both lorazepam alone and lorazepam with fluvoxamine produced substantial decrements in cognitive functioning; however, the co-administration of fluvoxamine and lorazepam did not produce larger mean decrements compared to lorazepam alone.

Methadone: Significantly increased methadone (plasma level:dose) ratios have been reported when fluvoxamine maleate was administered to patients receiving maintenance methadone

treatment, with symptoms of opioid intoxication in one patient. Opioid withdrawal symptoms were reported following fluvoxamine maleate discontinuation in another patient.

Sumatriptan: There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) is clinically warranted, appropriate observation of the patient is advised.

Tacrine: In a study of 13 healthy, male volunteers, a single 40 mg dose of tacrine added to fluvoxamine 100 mg/day administered at steady-state was associated with five- and eight-fold increases in tacrine Cmax and AUC, respectively, compared to the administration of tacrine alone. Five subjects experienced nausea, vomiting, sweating, and diarrhea following co-administration, consistent with the cholinergic effects of tacrine.

Thioridazine: See **CONTRAINDICATIONS** and **WARNINGS**.

Tricyclic Antidepressants (TCAs): Significantly increased plasma TCA levels have been reported with the co-administration of fluvoxamine maleate and amitriptyline, clomipramine or imipramine. Caution is indicated with the co-administration of LUVOX® Tablets and TCAs; plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced.

combination should, therefore, be used with caution. Severe vomiting has been reported with the co-administration of fluvoxamine maleate and tryptophan.

Other Drugs:
Theophylline: See **WARNINGS**

Warfarin: See **WARNINGS**

Digoxin: Administration of fluvoxamine maleate 100 mg daily for 18 days (N=8) did not significantly affect the pharmacokinetics of a 1.25 mg single intravenous dose of digoxin.

Diltiazem: Bradycardia has been reported with the co-administration of fluvoxamine maleate and diltiazem.

Propranolol and Other Beta-Blockers: Co-administration of fluvoxamine maleate 100 mg per day and propranolol 160 mg per day in normal volunteers resulted in a mean five-fold increase (range 2 to 17) in minimum propranolol plasma concentrations. In this study, there was a slight potentiation of the propranolol-induced reduction in heart rate and reduction in the exercise diastolic pressure.

One case of bradycardia and hypotension and a second case of orthostatic hypotension have been reported with the co-administration of fluvoxamine maleate and metoprolol.

If propranolol or metoprolol is co-administered with LUVOX® Tablets, a reduction in the initial beta-blocker dose and more cautious dose titration are recommended. No dosage adjustment is required for LUVOX® Tablets.

Co-administration of fluvoxamine maleate 100 mg per day with atenolol 100 mg per day (N=6) did not affect the plasma concentrations of atenolol. Unlike propranolol and metoprolol which undergo hepatic metabolism, atenolol is eliminated primarily by renal excretion.

Effects of Smoking on Fluvoxamine Metabolism: Smokers had a 25% increase in the metabolism of fluvoxamine compared to nonsmokers.

Electroconvulsive Therapy (ECT): There are no clinical studies establishing the benefits or risks of combined use of ECT and fluvoxamine maleate.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: There is no evidence of carcinogenicity, mutagenicity or impairment of fertility with fluvoxamine maleate.

There was no evidence of carcinogenicity in rats treated orally with fluvoxamine maleate for 30 months or hamsters treated orally with fluvoxamine maleate for 20 (females) or 26 (males) months. The daily doses in the high dose groups in these studies were increased over the course of the study from a minimum of 160 mg/kg to a maximum of 240 mg/kg in rats, and from a minimum of 135 mg/kg to a maximum of 240 mg/kg in hamsters. The maximum dose of 240 mg/kg is approximately 6 times the maximum human daily dose on a mg/m^2 basis.

Mutagenesis: No evidence of mutagenic potential was observed in a mouse micronucleus test, an *in vitro* chromosome aberration test, or the Ames microbial mutagen test with or without metabolic activation.

Impairment of Fertility: In fertility studies of male and female rats, up to 80 mg/kg/day orally of fluvoxamine maleate (approximately 2 times the maximum human daily dose on a mg/m^2 basis) had no effect on mating performance, duration of gestation, or pregnancy rate.

Pregnancy

Teratogenic Effects - Pregnancy Category C: In teratology studies in rats and rabbits, daily oral doses of fluvoxamine maleate of up to 80 and 40 mg/kg, respectively (approximately 2 times the maximum human daily dose on a mg/m^2 basis) caused no fetal malformations. However, in other reproduction studies in which pregnant rats were dosed through weaning there was (1) an increase in pup mortality at birth (seen at 80 mg/kg and above but not at 20 mg/kg), and (2) decreases in postnatal pup weights (seen at 160 but not at 80 mg/kg) and survival (seen at all doses; lowest dose tested = 5 mg/kg). (Doses of 5, 20, 80, and 160 mg/kg are approximately 0.1, 0.5, 2, and 4 times the maximum human daily dose on a mg/m^2 basis.) While the results of a cross-fostering study implied that at least some of these results likely occurred secondarily to maternal toxicity, the role of a direct drug effect on the fetuses or pups could not be ruled out. There are no adequate and well-controlled studies in pregnant women. Fluvoxamine maleate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of fluvoxamine on labor and delivery in humans is unknown.

Nursing Mothers

As for many other drugs, fluvoxamine is secreted in human breast milk. The decision of whether to discontinue nursing or to discontinue the drug should take into account the potential for serious adverse effects from exposure to fluvoxamine in the nursing infant as well as the potential benefits of LUVOX® (Fluvoxamine Maleate) Tablets therapy to the mother.

Pediatric Use

The efficacy of fluvoxamine maleate for the treatment of Obsessive Compulsive Disorder was demonstrated in a 10-week multicenter placebo controlled study with 120 outpatients ages 8-17. In addition, 99 of these outpatients continued open-label fluvoxamine maleate treatment for up to another one to three years, equivalent to 94 patient years. The adverse event profile observed in that study was generally similar to that observed in adult studies with fluvoxamine (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

Decreased appetite and weight loss have been observed in association with the use of fluvoxamine as well as other SSRIs. Consequently, regular monitoring of weight and growth is recommended if treatment of a child with an SSRI is to be continued long term.

The risks, if any, that may be associated with fluvoxamine's extended use in children and adolescents with OCD have not been systematically assessed. The prescriber should be mindful that the evidence relied upon to conclude that fluvoxamine is safe for use in children and adolescents derives from relatively short term clinical studies and from extrapolation of experience gained with adult patients. In particular, there are no studies that directly evaluate the effects of long term fluvoxamine use on the growth, development, and maturation of children and

adolescents. Although there is no affirmative finding to suggest that fluvoxamine possesses a capacity to adversely affect growth, development or maturation, the absence of such findings is not compelling evidence of the absence of the potential of fluvoxamine to have adverse effects in chronic use.

Geriatric Use

Approximately 230 patients participating in controlled premarketing studies with LUVOX® Tablets were 65 years of age or over. No overall differences in safety were observed between these patients and younger patients. Other reported clinical experience has not identified differences in response between the elderly and younger patients. However, fluvoxamine has been associated with several cases of clinically significant hyponatremia in elderly patients (see **PRECAUTIONS, General**). Furthermore, the clearance of fluvoxamine is decreased by about 50% in elderly compared to younger patients (see **Pharmacokinetics** under **CLINICAL PHARMACOLOGY**), and greater sensitivity of some older individuals also cannot be ruled out. Consequently, LUVOX® Tablets should be slowly titrated during initiation of therapy.

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Of the 1087 OCD and depressed patients treated with fluvoxamine maleate in controlled clinical trials conducted in North America, 22% discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate at least twice that of placebo) included:

Table 1

ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION OF TREATMENT IN OCD AND DEPRESSION POPULATIONS

BODY SYSTEM/ ADVERSE EVENT	PERCENTAGE OF PATIENTS FLUVOXAMINE	PLACEBO
BODY AS A WHOLE		
Headache	3%	1%
Asthenia	2%	<1%
Abdominal Pain	1%	0%
DIGESTIVE		
Nausea	9%	1%
Diarrhea	1%	<1%
Vomiting	2%	<1%
Anorexia	1%	<1%
Dyspepsia	1%	<1%
NERVOUS SYSTEM		
Insomnia	4%	1%
Somnolence	4%	<1%
Nervousness	2%	<1%
Agitation	2%	<1%
Dizziness	2%	<1%
Anxiety	1%	<1%
Dry Mouth	1%	<1%

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials:

LUVOX® Tablets have been studied in controlled trials of OCD (N=320) and depression (N=1350). In general, adverse event rates were similar in the two data sets as well as in the pediatric OCD study. The most commonly observed adverse events associated with the use of LUVOX® Tablets and likely to be drug-related (incidence of 5% or greater and at least twice that

for placebo) derived from Table 2 were: *somnolence, insomnia, nervousness, tremor, nausea, dyspepsia, anorexia, vomiting, abnormal ejaculation, asthenia, and sweating.* In a pool of two studies involving only patients with OCD, the following additional events were identified using the above rule: *dry mouth, decreased libido, urinary frequency, anorgasmia, rhinitis and taste perversion.* In a study of pediatric patients with OCD, the following additional events were identified using the above rule: *agitation, depression, dysmenorrhea, flatulence, hyperkinesia, and rash.*

Adverse Events Occurring at an Incidence of 1%: Table 2 enumerates adverse events that occurred in adults at a frequency of 1% or more, and were more frequent than in the placebo group, among patients treated with LUVOX® Tablets in two short-term placebo controlled OCD trials (10 week) and depression trials (6 week) in which patients were dosed in a range of generally 100 to 300 mg/day. This table shows the percentage of patients in each group who had at least one occurrence of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors may differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side-effect incidence rate in the population studied.

Table 2

TREATMENT-EMERGENT ADVERSE EVENT INCIDENCE RATES BY BODY SYSTEM IN ADULT OCD AND DEPRESSION POPULATIONS COMBINED[1]

	Percentage of Patients Reporting Event	
BODY SYSTEM/ ADVERSE EVENT	**FLUVOXAMINE N = 892**	**PLACEBO N = 778**
BODY AS WHOLE		
Headache	22	20
Asthenia	14	6
Flu Syndrome	3	2
Chills	2	1
CARDIOVASCULAR		
Palpitations	3	2
DIGESTIVE SYSTEM		
Nausea	40	14
Diarrhea	11	7
Constipation	10	8
Dyspepsia	10	5
Anorexia	6	2
Vomiting	5	2
Flatulence	4	3
Tooth Disorder[2]	3	1
Dysphagia	2	1
NERVOUS SYSTEM		
Somnolence	22	8
Insomnia	21	10
Dry Mouth	14	10
Nervousness	12	5
Dizziness	11	6
Tremor	5	1
Anxiety	5	3
Vasodilatation[3]	3	1
Hypertonia	2	1
Agitation	2	1
Decreased Libido	2	1
Depression	2	1

BODY SYSTEM/ ADVERSE EVENT	Percentage of Patients Reporting Event FLUVOXAMINE N = 892	PLACEBO N = 778
CNS Stimulation	2	1
RESPIRATORY SYSTEM		
Upper Respiratory Infection	9	5
Dyspnea	2	1
Yawn	2	0
SKIN		
Sweating	7	3
SPECIAL SENSES		
Taste Perversion	3	1
Amblyopia[4]	3	2
UROGENITAL		
Abnormal Ejaculation[5,6]	8	1
Urinary Frequency	3	2
Impotence[6]	2	1
Anorgasmia	2	0
Urinary Retention	1	0

[1] Events for which fluvoxamine maleate incidence was equal to or less than placebo are not listed in the table above, but include the following: abdominal pain, abnormal dreams, appetite increase, back pain, chest pain, confusion, dysmenorrhea, fever, infection, leg cramps, migraine, myalgia, pain, paresthesia, pharyngitis, postural hypotension, pruritus, rash, rhinitis, thirst and tinnitus.

[2] Includes "toothache," "tooth extraction and abscess," and "caries."

[3] Mostly feeling warm, hot, or flushed.

[4] Mostly "blurred vision."

[5] Mostly "delayed ejaculation."

[6] Incidence based on number of male patients.

Adverse Events in OCD Placebo Controlled Studies Which are Markedly Different (defined as at least a two-fold difference) in Rate from the Pooled Event Rates in OCD and Depression Placebo Controlled Studies: The events in OCD studies with a two-fold decrease in rate compared to event rates in OCD and depression studies were dysphagia and amblyopia (mostly blurred vision). Additionally, there was an approximate 25% decrease in nausea.

The events in OCD studies with a two-fold increase in rate compared to event rates in OCD and depression studies were: *asthenia, abnormal ejaculation (mostly delayed ejaculation), anxiety, infection, rhinitis, anorgasmia (in males), depression, libido decreased, pharyngitis, agitation, impotence, myoclonus/twitch, thirst, weight loss, leg cramps, myalgia and urinary retention.* These events are listed in order of decreasing rates in the OCD trials.

Other Adverse Events in OCD Pediatric Population

In pediatric patients (N=57) treated with LUVOX® Tablets, the overall profile of adverse events was generally similar to that seen in adult studies, as shown in Table 2. However, the following adverse events, not appearing in Table 2, were reported in two or more of the pediatric patients and were more frequent with LUVOX® Tablets than with placebo: abnormal thinking, cough increase, dysmenorrhea, ecchymosis, emotional lability, epistaxis, hyperkinesia, infection, manic reaction, rash, sinusitis, and weight decrease.

Male and Female Sexual Dysfunction with SSRIs

Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder and with aging, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRI's) can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence.

The table below displays the incidence of sexual side effects reported by at least 2% of patients taking Luvox in placebo controlled trials in depression and OCD.

Table 3

Percentage of Patients Reporting Sexual Adverse Events in Adult Placebo-Controlled Trials in OCD and Depression

	Luvox N=892	Placebo N=778
Abnormal Ejaculation*	8%	1%
Impotence*	2%	1%
Decreased Libido	2%	1%
Anorgasmia	2%	0%

* Based on the number of male patients.

There are no adequate and well-controlled studies examining sexual dysfunction with fluvoxamine treatment.

Fluvoxamine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae and upon discontinuation of fluvoxamine.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRI's, physicians should routinely inquire about such possible side effects.

Vital Sign Changes

Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) median change from baseline on various vital signs variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various vital signs variables revealed no important differences between fluvoxamine maleate and placebo.

Laboratory Changes

Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) median change from baseline on various serum chemistry, hematology, and urinalysis variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various serum chemistry, hematology, and urinalysis variables revealed no important differences between fluvoxamine maleate and placebo.

ECG Changes

Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) mean change from baseline on various ECG variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various ECG variables revealed no important differences between fluvoxamine maleate and placebo.

Other Events Observed During the Premarketing Evaluation of LUVOX® Tablets

During premarketing clinical trials conducted in North America and Europe, multiple doses of fluvoxamine maleate were administered for a combined total of 2737 patient exposures in patients suffering OCD or Major Depressive Disorder. Untoward events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a limited (i.e., reduced) number of standard event categories.

In the tabulations which follow, a standard COSTART-based Dictionary terminology has been used to classify reported adverse events. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. The frequencies presented, therefore, represent the proportion of the 2737 patient exposures to multiple doses of fluvoxamine maleate who experienced an event of the type cited on at least one occasion while receiving fluvoxamine maleate. All reported events are included in the list below, with the following exceptions: 1) those events already listed in Table 2, which tabulates incidence rates of common adverse experiences in placebo-controlled OCD and depression clinical trials, are excluded; 2) those events for which a drug cause was considered remote (i.e., neoplasia, gastrointestinal carcinoma, herpes simplex, herpes zoster, application site reaction, and unintended pregnancy) are omitted; and 3) events which were reported in only one patient and judged to not be potentially serious are not included. It is important to emphasize that, although the events reported did occur during treatment with fluvoxamine maleate, a causal relationship to fluvoxamine maleate has not been established.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring between 1/100 and 1/1000 patients; and rare adverse events are those occurring in less than 1/1000 patients.

Body as a Whole: *Frequent:* accidental injury, malaise; *Infrequent*: allergic reaction, neck pain, neck rigidity, overdose, photosensitivity reaction, suicide attempt; *Rare*: cyst, pelvic pain, sudden death.

Cardiovascular System: *Frequent*: hypertension, hypotension, syncope, tachycardia; *Infrequent*: angina pectoris, bradycardia, cardiomyopathy, cardiovascular disease, cold extremities, conduction delay, heart failure, myocardial infarction, pallor, pulse irregular, ST segment changes; *Rare:* AV block, cerebrovascular accident, coronary artery disease, embolus, pericarditis, phlebitis, pulmonary infarction, supraventricular extrasystoles.

Digestive System: *Frequent*: elevated liver transaminases; *Infrequent*: colitis, eructation, esophagitis, gastritis, gastroenteritis, gastrointestinal hemorrhage, gastrointestinal ulcer, gingivitis, glossitis, hemorrhoids, melena, rectal hemorrhage, stomatitis; *Rare*: biliary pain, cholecystitis, cholelithiasis, fecal incontinence, hematemesis, intestinal obstruction, jaundice.

Endocrine System: *Infrequent:* hypothyroidism; *Rare:* goiter.

Hemic and Lymphatic Systems: *Infrequent*: anemia, ecchymosis, leukocytosis, lymphadenopathy, thrombocytopenia; *Rare*: leukopenia, purpura.

Metabolic and Nutritional Systems: *Frequent:* edema, weight gain, weight loss; *Infrequent*: dehydration, hypercholesterolemia; *Rare:* diabetes mellitus, hyperglycemia, hyperlipidemia, hypoglycemia, hypokalemia, lactate dehydrogenase increased.

Musculoskeletal System: *Infrequent*: arthralgia, arthritis, bursitis, generalized muscle spasm, myasthenia, tendinous contracture, tenosynovitis; *Rare*: arthrosis, myopathy, pathological fracture.

Nervous System: *Frequent*: amnesia, apathy, hyperkinesia, hypokinesia, manic reaction, myoclonus, psychotic reaction; *Infrequent*: agoraphobia, akathisia, ataxia, CNS depression, convulsion, delirium, delusion, depersonalization, drug dependence, dyskinesia, dystonia, emotional lability, euphoria, extrapyramidal syndrome, gait unsteady, hallucinations, hemiplegia, hostility, hypersomnia, hypochondriasis, hypotonia, hysteria, incoordination, increased salivation, increased libido, neuralgia, paralysis, paranoid reaction, phobia, psychosis, sleep disorder, stupor, twitching, vertigo; *Rare:* akinesia, coma, fibrillations, mutism, obsessions, reflexes decreased, slurred speech, tardive dyskinesia, torticollis, trismus, withdrawal syndrome.

Respiratory System: *Frequent*: cough increased, sinusitis; *Infrequent*: asthma, bronchitis, epistaxis, hoarseness, hyperventilation; *Rare*: apnea, congestion of upper airway, hemoptysis, hiccups, laryngismus, obstructive pulmonary disease, pneumonia.

Skin: *Infrequent*: acne, alopecia, dry skin, eczema, exfoliative dermatitis, furunculosis, seborrhea, skin discoloration, urticaria.

Special Senses: *Infrequent*: accommodation abnormal, conjunctivitis, deafness, diplopia, dry eyes, ear pain, eye pain, mydriasis, otitis media, parosmia, photophobia, taste loss, visual field defect; *Rare*: corneal ulcer, retinal detachment.

Urogenital System**:** *Infrequent*: anuria, breast pain, cystitis, delayed menstruation[1], dysuria, female lactation[1], hematuria, menopause[1], menorrhagia[1], metrorrhagia[1], nocturia, polyuria, premenstrual syndrome[1], urinary incontinence, urinary tract infection, urinary urgency, urination impaired, vaginal hemorrhage[1], vaginitis[1]; *Rare*: kidney calculus, hematospermia[2], oliguria.

[1]Based on the number of females.

[2]Based on the number of males.

Postmarketing Reports Voluntary reports of adverse events in patients taking LUVOX® Tablets that have been received since market introduction and are of unknown causal relationship to LUVOX® Tablets use include: ventricular tachycardia (including torsades de pointes), porphyria, toxic epidermal necrolysis, Stevens-Johnson syndrome, Henoch-Schoenlein purpura, bullous eruption, priapism, agranulocytosis, aplastic anemia, anaphylactic reaction, angioedema, vasculitis, hyponatremia, acute renal failure, hepatitis, pancreatitis, ileus, serotonin syndrome, neuropathy, laryngismus, and severe akinesia with fever when fluvoxamine was co-administered with antipsychotic medication.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

LUVOX® Tablets are not controlled substances.

Physical and Psychological Dependence

The potential for abuse, tolerance and physical dependence with fluvoxamine maleate has been studied in a nonhuman primate model. No evidence of dependency phenomena was found. The discontinuation effects of LUVOX® Tablets were not systematically evaluated in controlled clinical trials. LUVOX® Tablets were not systematically studied in clinical trials for potential for abuse, but there was no indication of drug-seeking behavior in clinical trials. It should be noted, however, that patients at risk for drug dependency were systematically excluded from investigational studies of fluvoxamine maleate. Generally, it is not possible to predict on the basis of preclinical or premarketing clinical experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of fluvoxamine maleate misuse or abuse (i.e., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Worldwide exposure to fluvoxamine maleate includes over 45,000 patients treated in clinical trials and an estimated exposure of 23,000,000 patients treated during worldwide marketing experience (circa 1999). Of the 462 cases of deliberate or accidental overdose involving fluvoxamine maleate reported from this population, there were 44 deaths. Of these, six were in patients taking fluvoxamine maleate alone and the remaining 38 were in patients taking fluvoxamine maleate along with other drugs. Among non-fatal overdose cases, 373 patients had complete recovery; four patients experienced adverse sequelae of overdosage, to include persistent mydriasis, unsteady

gait, kidney complications (from trauma associated with overdose), and bowel infarction requiring a hemicolectomy. In the remaining 41 patients, the outcome was unknown. The largest known ingestion of fluvoxamine maleate involved 12,000 mg (equivalent to 2 to 3 months' dosage). The patient fully recovered. However, ingestions as low as 1,400 mg have been associated with lethal outcome, indicating considerable prognostic variability.

Commonly (≥5%) observed adverse events associated with fluvoxamine maleate overdose include coma, hypokalemia, hypotension, nausea, respiratory difficulties, somnolence, tachycardia and vomiting. Other notable signs and symptoms seen with fluvoxamine maleate overdose (single or multiple drugs) include, bradycardia, ECG abnormalities, (such as heart arrest, QT interval prolongation, first degree atrioventricular block, bundle branch block, and junctional rhythm), convulsions, tremor, diarrhea, and increased reflexes.

Management of Overdose

Treatment should consist of those general measures employed in the management of overdosage with any antidepressant.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for fluvoxamine are known.

A specific caution involves patients taking, or recently having taken, fluvoxamine who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see Tricyclic Antidepressants (TCAs) under **PRECAUTIONS**).

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION

Dosage for Adults

The recommended starting dose for LUVOX® Tablets in adult patients is 50 mg, administered as a single daily dose at bedtime. In the controlled clinical trials establishing the effectiveness of LUVOX® Tablets in OCD, patients were titrated within a dose range of 100 to 300 mg/day. Consequently, the dose should be increased in 50 mg increments every 4 to 7 days, as tolerated, until maximum therapeutic benefit is achieved, not to exceed 300 mg per day. It is advisable that a total daily dose of more than 100 mg should be given in two divided doses. If the doses are not equal, the larger dose should be given at bedtime.

Dosage for Pediatric Population (children and adolescents)

The recommended starting dose for LUVOX® Tablets in pediatric populations (ages 8-17 years) is 25 mg, administered as a single daily dose at bedtime. In a controlled clinical trial establishing the effectiveness of LUVOX® Tablets in OCD, pediatric patients (ages 8-17) were titrated within a dose range of 50 to 200 mg/day. Physicians should consider age and gender differences when dosing pediatric patients. The maximum dose in children up to age 11 should not exceed 200 mg/day. Therapeutic effect in female children may be achieved with lower doses. Dose adjustment in adolescents (up to the adult maximum dose of 300 mg) may be indicated to achieve therapeutic

benefit. The dose should be increased in 25 mg increments every 4 to 7 days, as tolerated, until maximum therapeutic benefit is achieved . It is advisable that a total daily dose of more then 50 mg should be given in two divided doses. If the two divided doses are not equal, the larger dose should be given at bedtime.

Dosage for Elderly or Hepatically Impaired Patients
Elderly patients and those with hepatic impairment have been observed to have a decreased clearance of fluvoxamine maleate. Consequently, it may be appropriate to modify the initial dose and the subsequent dose titration for these patient groups.

Maintenance/Continuation Extended Treatment
Although the efficacy of LUVOX® Tablets beyond 10 weeks of dosing for OCD has not been documented in controlled trials, OCD is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

HOW SUPPLIED

Tablets 25 mg: unscored, white, elliptical, film-coated (debossed "SOLVAY" and "4202" on one side)

Bottles of 100 NDC 0032-4202-01

Unit dose pack of 100 NDC 0032-4202-11

Tablets 50 mg: scored, yellow, elliptical, film-coated (debossed "SOLVAY" and "4205" on one side and scored on the other)

Bottles of 100 NDC 0032-4205-01

Bottles of 1000NDC 0032-4205-10

Unit dose pack of 100 NDC 0032-4205-11

Tablets 100 mg: scored, beige, elliptical, film-coated (debossed "SOLVAY" and "4210" on one side and scored on the other)

Bottles of 100 NDC 0032-4210-01

Bottles of 1000NDC 0032-4210-10

Unit dose pack of 100 NDC 0032-4210-11

LUVOX® Tablets should be protected from high humidity and stored at controlled room temperature, 15°-30° C (59°-86° F).

Dispense in tight containers.

Solvay

Pharmaceuticals, Inc.

Marietta, GA 30062